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Editorial

A Randomized Controlled Trial of Fecal Microbiota Transplantation for Parkinson's Disease: Getting it right, if not PARFECT

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The role of the gut microbiome in Parkinson's disease (PD) has rightfully gained extensive scientific interest in recent years. Numerous aspects of the disease have been linked to the intestinal microbiome: the pathogenesis of the disease itself [1], the clinical phenotype [2], the effect of levodopa [3] and – when used as a target for intervention – symptomatic [4] or possibly even disease-modifying effects [5]. This interventional aspect was brought further to the fore by the recent publication of the GUT-PARFECT study by Bruggeman and colleagues in *eClinicalMedicine*, describing the results of a single-center fecal microbiota transplantation (FMT) trial in persons with relatively early-stage PD [6].

FMT entails the transplantation (via various possible delivery routes) of a fecal microbiota concentrate prepared from donor stool. Currently, recurrent or refractory *Clostridioides difficile* infection is the only registered indication [7]. In recent years, an increased focus on the link between PD and the gut microbiome has prompted several trials of FMT in people with PD (PwP), two of which were randomized and placebo-controlled. These two studies had either a small sample size ($n = 12$) [8] or a relatively short follow-up duration (12 weeks) [9]; there was minimal or no statistically significant improvement of the MDS-UPDRS part III (motor) scores.

Bruggeman and colleagues are to be commended for having now performed a well-designed, double-blind, placebo-controlled phase 2 study in a fair number of participants ($n = 46$). Those in the active arm received a single healthy-donor FMT treatment, whereas controls in the placebo arm received a single autologous FMT treatment. The results showed a statistically significant change in MDS-UPDRS part III scores in the OFF state for FMT from healthy donors compared with placebo after 12 months (primary outcome measure). The effect size was small, however, showing a reduction of 5.8 points in the FMT arm as compared to a reduction of 2.7 in the placebo arm (between-group difference of 3.1 points; about as large as the baseline difference between both treatment arms). The treatment was well-tolerated, so adverse effects did not unblind the participants

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(although the paper does not state whether they were formally debriefed at the end of the study).

The design and execution of this study are its primary strengths. Based upon the inclusion and exclusion criteria, the external validity appears to be good. The follow-up duration of 12 months after the intervention is an adequate start for assessing long-term effects. Drop-out was limited, as were missing data. However, several critical notes are worth mentioning.

First, the placebo effect was rather large, with a mean MDS-UPDRS OFF motor score *reduction* of 2.7 in the control group, whereas the authors note that a 6.35 point *increase* would have been expected based upon natural disease progression. Perhaps the placebo effect was amplified by inadvertent selection bias favoring strongly motivated participants. This possibility is highlighted by the fact that as many as 99 potential participants either refused the intervention or withdrew their consent. As a result, the relative (between-group) reduction in motor scores was only 3.1 points (5.8–2.7), which is below the minimal clinically important difference (MCID) of 3.25. Of note, the authors correctly mention that the MCID was originally described by Horváth et al. in reference to a within-patient difference [10]; however, in order to determine clinical superiority over placebo in a clinical trial setting, we feel that the relevant outcome measure is the between-group difference. The clinical relevance to PwP is therefore not immediately obvious from this study, although longer follow-up may demonstrate larger differential effect sizes.

Second, the investigators assessed many parameters (including colonic transit time at four different time points) yet they did not opt for microbiome analysis, neither in stool of the participants nor in the donor stool. This is a significant omission given the authors' inference that they demonstrated "a disease modifying effect of gut microbiota alteration" without testing whether their intervention did, in fact, alter the participants' gut microbiota or whether these alterations differed between treatment groups. Any mechanistic inference would need to include a demonstration of treatment-group-specific microbiome compositional changes (either within patients or between groups) at the 12-month timepoint. Further, microbiome analysis could also assist in uncovering potential confounding factors in the trial such as collection of stool before (from healthy donors) versus during (PwP/placebo) the COVID-19 pandemic.

Third, Bruggeman and colleagues interpret their findings as being reflective of a possible disease-modifying effect. However, we disagree with this interpretation based upon several considerations. The MDS-UPDRS motor scores improved in both groups, consistent with a symptomatic improvement. Based upon the study design, it is impossible to separate such a symptomatic effect from any underlying disease-modifying mechanism. Biomarkers of neurodegeneration, such as dopamine neuroimaging and CSF- or blood-based biomarkers, were not included in this study. Moreover, the levodopa-equivalent daily dose increased by a similar magnitude in both the intervention and placebo arms, belying the notion of disease modification. In fact, a viable hypothesis is that FMT indirectly affected PD symptoms via a modulating effect on levodopa's long-duration response, which is still measurable 8 hours after levodopa cessation. The significant improvement in colonic transit time observed by the authors may (through attenuation of the *cologastric brake*) [3] have resulted in improved levodopa bioavailability. In a population already using levodopa, complete elimination of levodopa-associated confounding effects is difficult, given the ethical issues associated with asking levodopa-dependent participants to stop taking this for months to eliminate the long-duration response.

In future research, it would be interesting to replicate this study in a drug-naïve early PD population. An interesting co-variate could be fecal tyrosine decarboxylase (TDC) activity. This bacterially-produced enzyme is able to prematurely metabolize levodopa in the gut, diminishing its bioavailability [3]. In levodopa users, it is conceivable that at least part of the efficacy of FMT on PD symptoms could be explained by a reduction of the abundance of TDC-producing bacteria and a consequent increase in levodopa bioavailability. Performing suprathreshold-dose ON-state measurements in participants, in addition to OFF-state measurements, could also provide insight into a hypothetical potentiating influence of FMT on the effect of levodopa. Testing for TDC activity before and after FMT, as well as investigating the presence of small-intestinal bacterial overgrowth (SIBO, possibly a prerequisite for clinically-relevant TDC-mediated premature levodopa metabolization), could accompany this. In fact, one previous small FMT trial in PwP used a positive breath test for SIBO as an inclusion criterion and demonstrated normalization of the breath test after FMT in all 11 participants [11].

For future trials, outcome biomarkers such as dopamine neuroimaging (DaT-SPECT) or aromatic *L*-amino acid decarboxylase [12] (AADC, also known as DOPA decarboxylase) may be considered to gather converging evidence for a modifying effect of FMT on dopaminergic neurodegeneration. Other mechanistic parameters, such as biomarkers of intestinal inflammation and permeability, might provide additional insight.

In addition to providing mechanistic information, analyzing the microbial composition of participants' stool may provide a rationale for selection of patients with potential responsiveness to FMT. This may also help in preferentially selecting participants with body-first vs. brain-first PD (the authors did touch upon this, but did not analyze these phenotypes in depth). Microbiota analysis of donor stool might well prove to be important as well, as even 'healthy' donor stool could potentially contain bacterial strains that are detrimental to PwP, such as TDC-producing strains. A recently completed, but yet unpublished Finnish study into FMT for PwP (NCT04854291) used intestinal dysbiosis as an inclusion criterion; the results may provide an insight into whether this strategy improves the chance of meeting clinical endpoints.

In conclusion, further research into FMT as a potential treatment in PD is warranted. The fact that it is well tolerated is an important aspect in this regard. With the currently available evidence, it cannot yet be concluded whether its effect in humans constitutes neuroprotection or merely confers long-lasting symptomatic benefit, and whether this benefit is actually large enough to be clinically relevant. Also, further research is necessary to determine whether selection of FMT candidates (and selecting the optimal donor stool) should be based upon microbiome parameters and whether it is equally effective for body-first vs. brain-first PwP.

In the meantime, the effect of media attention for FMT studies is already noticeable in clinical practice. So what should a movement disorders neurologist answer to a PwP enquiring about the possibility of undergoing FMT treatment? As FMT is a clinically available treatment – registered for the therapy of certain *C. difficile* infections – one might feel tempted to prescribe it 'off-label' to PwP. However, we feel that this should be avoided. Given the state of the evidence thus far, patience should be exercised and PwP should be educated on the uncertainties still surrounding FMT for PD. They could also be motivated to engage in further research which will ultimately inform future clinical practice.

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